Human Papillomavirus (HPV), Cervical Dysplasia and HPV Vaccination

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Disclosures

- Consultant for:
  - Merck
  - Orthobiotech

The Papanicolaou Test

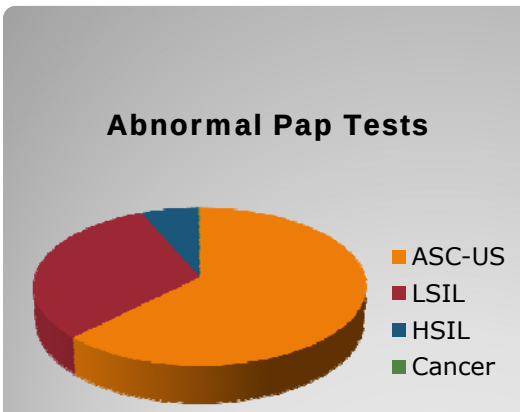
- Developed by Drs. Papanicolaou and Traut in the 1940s
- Consists of collecting cervical cytology from the cervix and depositing them onto a slide for microscopic evaluation
- Easy to collect and objectively interpret results
- Initially used to detect cervical cancer

Papanicolaou and Traut: Diagnosis of uterine cancer by the vaginal smear, 1943

The Papanicolaou Test

- The Pap test has dramatically decreased the incidence and mortality rate of cervical cancer in the United States
  - US - 11,150 new cases each year
    - 3,700 deaths annually from cervical cancer
  - Worldwide 493,000 new cases
    - 293,000 deaths annually worldwide

Parkin et al. Int J Cancer, 2005.
Jemal et al. CA, 2007



The Papanicolaou Test

Estimated 50 million Pap tests performed in the US

5% will be diagnosed as abnormal

2-3 million ASC-US Pap tests

1.5 million LSIL Pap tests

300,000 HSIL Pap tests

- 50% of women diagnosed with cervical cancer have not had a pap test in 5 years
- 25% of all cervical cancers are diagnosed in women older than 65
- In women older than 65, it is estimated that over 50% have not had a pap test in the past 10 years
- Bottom Line – the majority of women with cervical cancer fail to get annual pap tests

Who Develops Cervical Cancer?

Overview

- Bethesda 2001 nomenclature
- Human papillomavirus (HPV)
  - Types of HPV
  - Incidence of HPV
  - Incidence of HPV in cervical cancer
  - Mechanism for oncogenesis
  - Associated risk of cervical cancer with smoking
- Screening guidelines for cervical cancer
- 2006 ASCCP consensus guidelines for the management of abnormal Pap tests
- 2006 ASCCP consensus guidelines for the treatment of cervical dysplasia
- Types of treatment
- Screening intervals after treatment
- HPV vaccines

2001 Bethesda Nomenclature, squamous cells

- Mild dysplasia
  - **HPV** effect
  - **ASC-US** (Atypical Squamous Cells of Unknown Significance)
  - **LSIL** (Low Grade Squamous Intraepithelial Lesion)
- Severe dysplasia
  - **ASC-H** (Cannot rule out HGSIL)
  - **HSIL** (High Grade Squamous Intraepithelial Lesion)
  - **CIS** (Squamous Carcinoma In-Situ)

Solomon et al. JAMA, 2002.

- Glandular abnormalities
  - Benign appearing endometrial cells in a woman >40
  - **AGC** (Atypical Glandular Cells of Unknown Significance)
  - **AIS** (Adenocarcinoma In-Situ)
  - Adenocarcinoma
- AGC and AIS should be handled with utmost caution

2001 Bethesda Nomenclature, glandular cells

Solomon et al. JAMA, 2002.

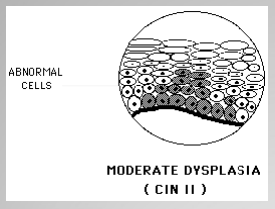
- Cytology pertains to a sample of cells
  - Pap test
- Histology pertains to a tissue sample
  - Colposcopic biopsy
- Cervical intraepithelial neoplasia (CIN) is the nomenclature used for colposcopic/cervical biopsies
- Cervical intraepithelial neoplasia (CIN) and dysplasia are synonymous

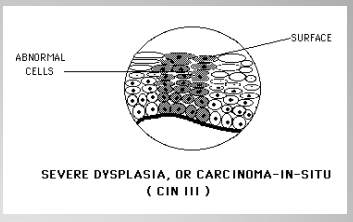
Cytology vs. Histology

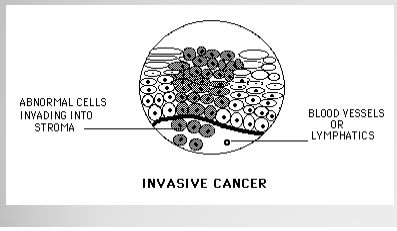
Dysplasia

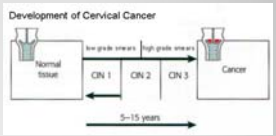
- Dysplasia is the pathologic term for preinvasive disease
- Dysplasia represents the ***POTENTIAL*** for abnormal cells to progress to invasive cancer
- This potential is subdivided
  - CIN 1 = mild dysplasia
  - CIN 2 = moderate dysplasia
  - CIN 3 = severe dysplasia
  - Carcinoma in situ and CIN 3 are the same

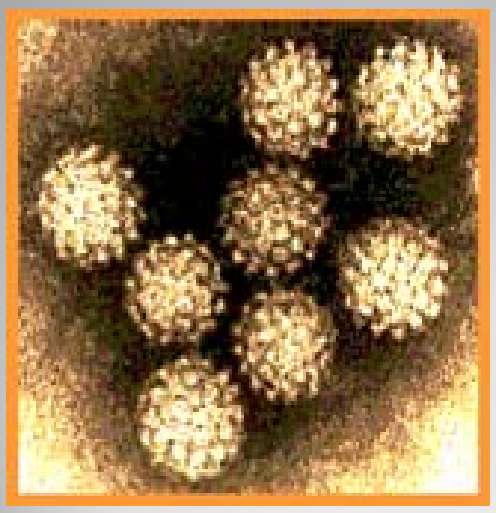
Anatomy of Dysplasia











Human Papillomavirus

- Member of the Papovaviridae family
- Double Stranded DNA tumor virus
- 45-55 nm icosohedral capsid
- More than 100 types
- Specific for target epithelium
- Epitheliotrophic and causes proliferation

HPV and types of infection

- **Mucocutaneous**
  - Verruca plantaris 1,2,4
  - Verruca vulgaris 2,4,29,38
  - Verruca plana 3,10,28
- **Anogenital**
  - Condyloma 6,11
  - Dysplasia and Cancer 16,18,31,33,35,45,51,56

Incidence of HPV

- 608 college-aged women studied from 1992-1994
- Followed 3 years at 6 month intervals
- Incidence of infection 43%
- Median duration of any HPV infection, 8 months
- 70% cleared in one year, 90% in two years

Ho et al. NEJM 1998

Risk Factors for HPV

- African American and Hispanic races **(RR 4.4 and 2.1)**
- Alcohol consumption >4 times a month **(RR 2)**
- >2-3 sexual partners in one year **(RR 3)**
- >6 sexual partners of main regular partner **(RR 10.1)**

Ho et al. NEJM 1998

- Most common types are high risk types 51,66,16,18
  - Type 16 found in 7% of 514 women
  - Type 18 found in 4% of 525 women

Incidence of HPV Types

Ho et al. NEJM 1998

- Persistent HPV more likely to progress to dysplasia
- High risk types take longer to clear (Median of 12 month)
- Women infected with high risk types documented at two 6 month visits were 38 times more likely to develop dysplasia

HPV and Cervical Dysplasia

Ho et al. NEJM 1998

Incidence of HPV types

- HPV 16 most common
  - Ho, et al. 7%
  - Kuhn, et al. 6%
  - Winer, et al. 10%
  - Richardson, et al. 8%
- HPV 18
  - Roughly 3-4%
- HPV 33, 39
  - Roughly 3-4%

HPV and cervical cancer

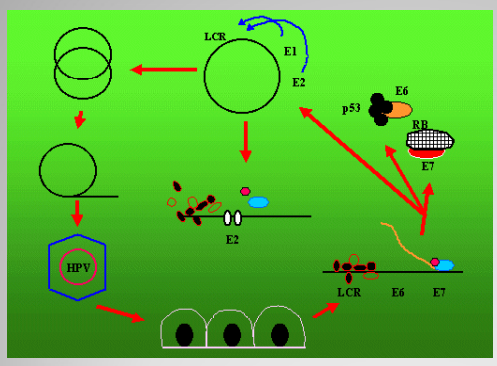
- Bosch, et al., in 1995, accrued 932 cases of cervical cancer from around the world
- Using polymerase chain reactions (PCR), his group amplified HPV DNA from the tumor and recorded their findings
- 93% of cervical carcinoma had HPV DNA
- Common types included 16, 18, 31, 33, 35, 39, 45, 51 (high risk HPV subtypes)

Bosch et al. J Natl Cancer Inst, 1995

- Walboomers, et al., repeated Bosch's experiment using new PCR primers
- Those cancers that failed to test positive for HPV DNA were retested with these new primers
- Results showed that 99.7% of Bosch's original cases tested positive for HPV DNA

HPV and cervical cancer

Walboomers et al. J Pathol, 1999



HPV and oncogenesis

- Viral DNA E6 and E7 believed to be crucial in stimulating cellular proliferation
- E6 acts by inhibiting p53 which is a crucial cell protein involved in programmed cell death (apoptosis)
- E7 acts by binding the retinoblastoma (Rb) protein
- Once bound, Rb releases E2F transcription factor which causes cellular proliferation
- Combined they inhibit the regulatory mechanism for apoptosis while stimulating the cell to proliferate

HPV and Smoking

- Prior to understanding the role of HPV in cervical cancer, studies which focused on smoking as a risk factor were often contradictory
- Once stratified for HPV status, many recent studies have shown that smokers with HPV are more likely to develop cervical cancer and CIN 3

Smoking and HPV

Smoking and Oncogenesis

- Two probable causes for oncogenesis
  - Accumulation of carcinogens from tobacco smoke in cervical mucous
  - Decreased host immune system
    - Decreased T cells more likely to lead to uncontrolled cell growth

Smoking and cervical cancer

- Plummer, et al., and the IARC performed a case-control study to determine if smoking was a cofactor for progression of HPV to cancer
- Included
  - 1463 squamous cell carcinomas
  - 124 adenocarcinomas
  - 211 CIN 3 cases
  - 254 control women
- Only women positive for HPV DNA were included

Plummer et al. Cancer Causes Control, 2003

- Results
  - Ever smoking and HPV had an **OR 2.17** (95% CI 1.46-3.22)
  - Stronger risk for squamous cell carcinomas **OR 2.3** (95% CI 1.31-4.04)
  - Ex-smokers also had an increased risk for developing squamous cell carcinoma, **OR 1.8** (95% CI 0.95-3.44)
  - No increased risk for smoking and adenocarcinoma

Smoking and cervical cancer

- The ALTS group examined smoking as a risk factor for developing CIN 3 or cervical cancer
- Included
  - 5,060 women with ASC-US or LSIL Pap tests
  - 3,133 women with high risk HPV
  - 506 women with CIN 3 or cancer

Smoking and CIN 3

McIntyre-Seltman et al. Cancer Epidemiol Biomarkers Prev, 2005

- Concluded
  - Current smokers (**OR 1.7**) and ex-smokers (**OR 1.7**) had a mildly increased risk for developing >CIN 3
  - Women who smoked more cigarettes and who smoked for a longer duration were at a higher risk for developing >CIN 3
  - Smoked more than 2 packs per day **OR 3.3** (95% CI 1.5-7.5)
  - Smoked greater than 11 years **OR 2.1** (95% CI 1.5-2.9)
  - Both the smoking duration and smoking intensity trended towards significance (Ptrend <0.0005)

Smoking and CIN 3

Source	Commencement	Interval < 30	High risk factors	Interval > 30 (3 consecutive negative Pap tests)	Cease
American Cancer Society (2002)	3 years after coitarche or no later than age 21	Every 2 years (liquid cytology) Annually (conventional)	Any abnormal Pap test HPV HIV GC or Chlamydia	Every 3 years	Women > 70 with normal Pap tests Hysterectomy for benign gynecologic reasons
American College of Obstetrics and Gynecology (2003)	3 years after coitarche or no later than age 21	***Annually***	Prior diagnosis of CIN 2 or 3 Immunocompromised HIV DES exposure	Every 2-3 years	***Physician discretion***

Screening guidelines

- Women who have had a hysterectomy for CIN 2 or 3
- Need Pap test every year until three consecutive normal Pap tests
- Incidence of vaginal dysplasia is 20% following a hysterectomy for CIN 2-3

Screening guidelines

- HPV testing can be used alone or in conjunction with cervical cytology for screening in women >30
  - Pooled sensitivity and specificity in women in North America and Europe for CIN 2 or greater
    - HPV testing: 95% and 93%
    - Cytology (ASC-US): 60% and 97%
    - Both: 99% and 99% (negative predictive value 99-100%)

Screening guidelines

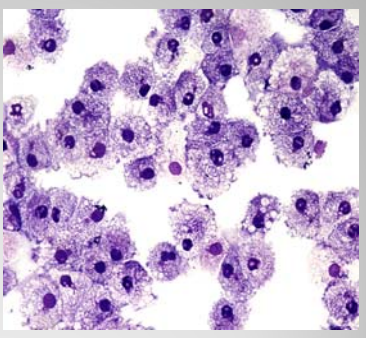
Cuzick et al. Int J Cancer. 2006

- Clinical implications for combined screening in women >30
- Both cytology and HPV testing are negative
  - Rescreen in no less than 3 years
  - 1/1000 risk of developing CIN 2 or greater
  - Wright et al. Obstet Gynecol. 2004
  - Kjaer et al. Cancer Res. 2006
  - Khan et al. J Natl Cancer Inst. 2005
- Negative cytology but positive HPV testing
  - Rescreen with cytology and HPV in 1 year
  - Risk of undetected CIN 2 or greater is 2.4-5.1%
  - Ronco et al. J Natl Cancer Inst. 2006
  - Bigras et al. Br J Cancer. 2005
  - Cuzick et al. Lancet. 2003
  - Clavel et al. Br J Cancer. 2001

Screening guidelines

Atypical Squamous Cells of Unknown Significance (ASC-US)

- COMMON
- 5% of all Pap tests
- 2-3 million/year
- CIN 1, 2, 3: 20-30%
- CIN 2, 3: 5-17%
- Carcinoma: 0.1-0.2%



Wright et al. Am J Obstet Gynecol, 2007.

ALTS Trial

- Multicenter, prospective, randomized controlled study
- Took 3488 ASC-US referrals
- Each patient had thin prep and HPV typing prior to randomly being assigned a study arm
- Placed into three arms
  - Colposcopy
  - Colposcopy for positive HPV test
  - Colposcopy for HSIL cytology

Solomon et al. JNCI 2001

Testing for HPV

- HPV is obtained with a cytobrush
- Hybrid capture II® (Digene®) is the commercial test
- Detects 13 high risk strains (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)
- Positive test > 1pg/ml of DNA content

Kuhn et al, J Natl Cancer Inst 2000

- All referral Pap tests brought before pathology review board for quality control
- 3,389 Pap tests analyzed by this board
  - 55% concurred ASC-US
  - 45% changed !!!
    - 31% NORMAL
    - 14% LSIL

ALTS

Solomon et al. JNCI 2001

- Colposcopy
- Normal 539 (62.9%)
- CIN 1 167 (19.5%)
- CIN 2 72 (7.4%)
- CIN 3 59 (6.9%)
- N 857
- 35% are CIN

- HPV screening
- Normal 237 (48%)
- CIN 1 111 (22.5%)
- CIN 2 59 (11.9%)
- CIN 3 77 (15.6%)
- N 494
- 50% are CIN

ALTS

Solomon et al. JNCI 2001

- 136 patients with CIN 3 in both arms
  - 125 women were HPV positive
  - Sensitivity 96.3%
  - PPV 10%
  - NPV 99.5%

ALTS

Solomon et al. JNCI 2001

ASC-US

- Benefit is NPV 99.5%
- Clinical Implications: If a patient is negative for high risk HPV then it is highly unlikely she will have CIN 3
- Therefore: colposcopy and biopsies are unlikely to yield CIN3

ASC-US management

- 1) Repeat Pap test in 6 months
  - If ASC-US or greater - Colposcopy
  - If normal repeat in 6 months; continue until two normal Pap tests are achieved then place patient on yearly Pap tests
- 2) Reflex HPV testing
  - If HPV positive – Colposcopy
  - If HPV negative – repeat Pap test in one year
- 3) Colposcopy

Wright et al. Am J Obstet Gynecol. 2007

ASC-US: special populations

- Adolescents (<20)
  - Repeat cytology in 1 year
  - No HPV testing (high prevalence would send most to colposcopy)
- Immunosuppressed
  - Follow general guidelines
- Pregnant woman
  - Follow general guidelines
  - Colposcopy can be performed 6 weeks *post-partum*

Wright et al. Am J Obstet Gynecol. 2007

ASC-H

- Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion
- ***NOT ASC-US!!!!***
- Pap test lacks conclusive cytology to be labeled as HSIL
- Significant rate of CIN 2-3 diagnosed on colposcopic biopsies (40%)
- High Risk HPV 85%

ASC-H management

- COLPOSCOPY
  - If colposcopy and biopsies are normal…
  - Repeat Pap test in 6 and 12 months
  - Or HPV testing in 12 months

- 1.5 million/year
- Usually histology confirms CIN 1
- 76% of LSIL Pap tests are positive for high risk HPV
  - Metaanalysis: Arbyn et al. Vaccine. 2006
- Colposcopy is the initial management

Low Grade Squamous Intraepithelial Lesion (LSIL)

- Colposcopy
- Prevalence of CIN 2 or greater 12-16%
  - Alvarez et al. Gynecol Oncol. 2007
  - Chute et al. Diagn Cytopathol. 2006
  - Solomon et al. JNCI. 2001

LSIL management

LSIL: special populations

- Adolescents (<20)
  - Repeat cytology in 1 year
  - No HPV testing
  - At 12 months colposcopy for HSIL
  - At 24 months colposcopy for ASC-US or greater
- Postmenopausal women
  - HPV testing
  - Or Pap testing at 6 and 12 months
- Pregnant woman
  - Colposcopy
  - If no evidence of CIN 2,3 or cancer then follow-up cytology post partum

Wright et al. Am J Obstet Gynecol. 2007

High Grade Squamous Intraepithelial Lesion (HSIL)

- The most aggressive type of squamous cell dysplasia before invasive cancer
- HSIL rate 0.7%
- Colposcopy identifies 53-66% of women with CIN 2 or greater
- Loop electrosurgical excision procedure (LEEP) identifies 84-97% of women with CIN 2 or greater

Wright et al. Am J Obstet Gynecol. 2007

- 1) Colposcopy
- 2) LEEP

HSIL management

Wright et al. Am J Obstet Gynecol. 2007

- Adolescents (<20)
  - Colposcopy
  - If no CIN 2,3 is identified ***histologically***… observe with colposcopy and cytology (q 6 months) for 24 months
  - If HSIL persists and biopsies reveal no evidence of CIN 2 or greater after 24 months…LEEP
- Pregnant woman
  - Colposcopy
  - No excisional therapy unless cancer
  - Follow-up cytology and colposcopy 6 weeks *post partum*

HSIL: special populations

Wright et al. Am J Obstet Gynecol. 2007

- Rate 0.5-1.8%
- Rarely associated with significant pathology
- Follow clinical history
  - If obese and having abnormal bleeding consider an endometrial biopsy
  - If no symptoms…observe
- Caveat - benign appearing endometrial cells in a woman >40 in a ***postmenopausal*** woman ***ARE*** associated with significant endometrial pathology i.e. ***CANCER***

Benign appearing endometrial cells in a women >40

Greenspan et al. J Low Genit Tract Dis. 2006

- Old Bethesda system AGC was known as AGUS
- ***AGC*** was created to clear confusion between ***ASC-US*** and ***AGUS***
- ***THE TWO ARE NOT THE SAME !!!***
- Incidence is 0.1 to 1.5% of all Pap tests
- High risk HPV correlated with 38% of AGC Pap tests
- HPV testing not recommended

Atypical Glandular Cells (AGC)

Derchain et al. Gyn Oncol, 2004.

AGC

- AGC is worrisome for several pathologies: CIN, adenocarcinoma in situ, cervical adenocarcinoma and endometrial adenocarcinoma
- Many studies have documented the incidence of these disease processes
- AGUS system
  - Eddy et al. 36%, 1997 Am J Obstet Gynecol
  - Duska et al. 34%, 1998 Obstet Gynecol
  - Veljovich et al. 32%, 1998 Am J Obstet Gynecol
  - Manetta et al. 45%, 1999 Gynecol Oncol
  - Tam et al. 31%, 2003 Gynecol Oncol
- AGC system
  - DeSimone et al. 38%, 2006 Obstet Gynecol

AGC management

- 1) Colposcopy with or without biopsies
- 2) An endocervical curettage (ECC)
- 3) Endometrial biopsy in women with menorrhagia or age greater than 35

Wright et al. Am J Obstet Gynecol. 2007

AGC management

- Does every patient need an endometrial biopsy?
- Age is important
- Premenopausal women more likely to have HSIL vs. postmenopausal women (30.4% vs. 7.4%) p=0.04 Duska et al. Obstet Gynecol, 1998.
- Women over the age of 40 were more likely to have adenocarcinoma than dysplasia (31% vs. 6%) p=0.002 DeSimone et al. Obstet Gynecol, 2006

Adenocarcinoma in-situ (AIS)

- Aggressive form of dysplasia for columnar cells
- AIS cytology associated with
  - AIS histology (48-69%)
  - Cervical adenocarcinoma (38%)

Lee et al. Diagn Cytopathol, 1995.

- AIS cytology mandates colposcopic biopsies and an ECC
- AIS histology is managed with a cold knife cone (CKC)
- Numerous studies support CKC over loop electricosurgical excision procedure (LEEP) because of margin status
- CKC has fewer positive margins than LEEP
- Women with positive margins have 40-70% risk of residual AIS
- Women with negative margins have a 20 to 40% risk of residual AIS

AIS

- Recommend referral to GYN or GYN oncologist
- Nulliparous women are difficult to manage secondary to a high risk of residual disease
- Don’t underestimate the risk of invasive adenocarcinoma with an AIS Pap test

AIS

- CIN 1 often corresponds with ASC-US or LSIL Pap tests
- High rate of regression to normal
  - 90% regression among Brazilian women within 24 months Schlecht et al. J Natl Cancer Inst. 2003
  - 70% regression among Dutch women within 48 months Nobbenhuis et al. Lancet. 2003
  - 91% regression rate among adolescents within 36 months Moscicki et al. Lancet. 2004
- Low rate of progression to CIN 2,3
  - 12% in 24 months Cox et al. Am J Obstet Gynecol. 2003

CIN 1

- CIN 1 progressing to invasive cervical carcinoma
  - 0.1% in 2 years
  - 0.3% in 5 years
  - 1.6% in 10 years

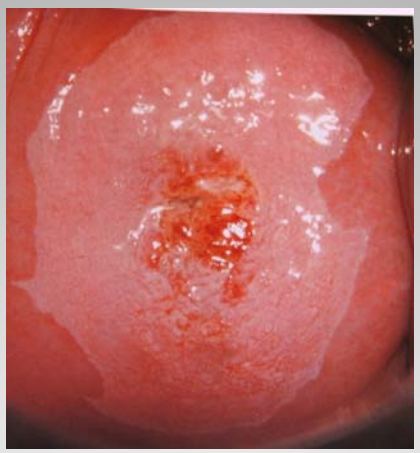
Progression of CIN 1

Holowaty et al. JNCI 1999

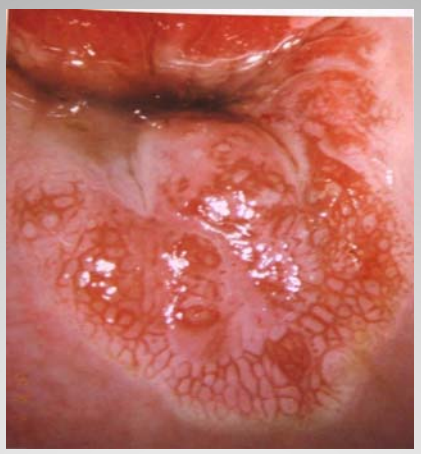
CIN 1 Colposcopic Findings

- Acetyl white plaques
- Bright white
- Clearly demarcated
- Fine punctations

- Acetic Acid - more is better



LSIL Pap and Colposcopy



LSIL Pap with Colposcopy

- CIN 1 *preceded* with ASC-US, ASC-H or LSIL
- **OBSERVATION**
  - Cervical cytology at 6 and 12 months
  - Or HPV testing in 12 months
  - If repeat cytology is ASC-US or greater or HPV is positive…repeat colposcopy
- Persistence of CIN 1 for 24 months…LEEP
- Podophyllin for treatment is unacceptable
- Hysterectomy as primary and principle treatment is unacceptable

CIN 1 management

CIN 1 management

- CIN 1 *preceded* by HSIL
- 1) LEEP
- 2) Colposcopy and cytology at 6 month intervals
  - If repeat cytology is still HSIL…LEEP

CIN 1 special populations

- Adolescents (<20)
  - ***Observation***
    - Repeat cytology in 12 months
    - At 12 months colposcopy for HSIL
    - At 24 months colposcopy for ASC-US or greater
  - No HPV testing
- Pregnant Women
  - Follow-up with cytology 6 weeks post partum

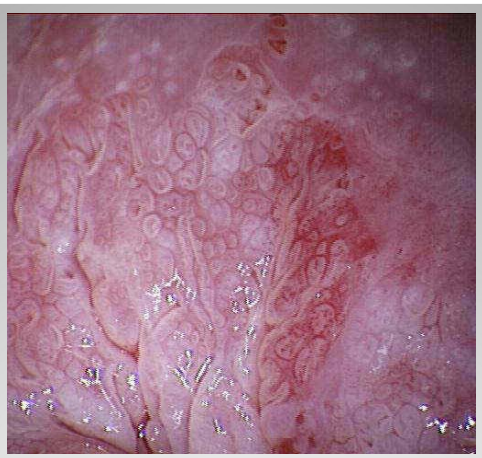
CIN 2, 3

- CIN 2, 3 often corresponds with ASC-H and HSIL Pap tests
- CIN 3 will progress to carcinoma if left untreated
  - 12% in 2 years
  - 70% in 8 years

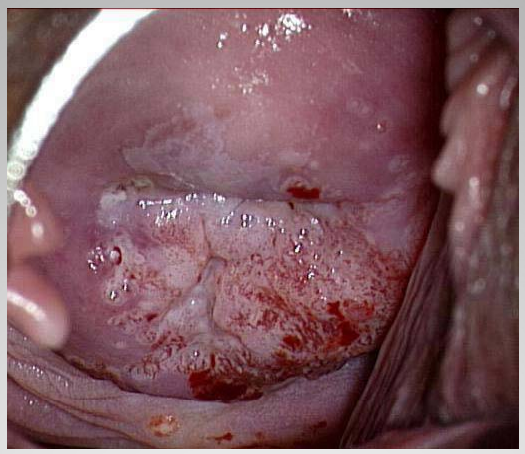
Holowaty et al. JNCI 1999

CIN 2, 3 Colposcopic Findings

- Dull acetyl white plaques
- Cobblestoning
- Coarse punctations
- Atypical vessels
- Mosaicism



HSIL Pap and Colposcopy



HSIL Pap and Colposcopy

CIN 2, 3 management

- LEEP
  - Hysterectomy is unacceptable for primary treatment
  - Positive margins follow LEEP should be observed with repeat cytology in 6 months
  - Hysterectomy is an acceptable treatment for recurrent CIN 2, 3

CIN 2, 3 special populations

- Adolescents (<20)
  - 1) Colposcopy and cytology at 6 month intervals for up to 24 months or..
  - 2) LEEP
- Pregnant Women
  - Colposcopy during pregnancy is acceptable to ensure lesion does not progress to carcinoma
  - 6 weeks post partum repeat colposcopy and cytology

Treatment Modalities

- Cryosugery
- Loop Electricosurgical Excision Procedure (LEEP)
- Laser Ablation
- Cold Knife Conization
- Hysterectomy

Cryosurgery

- Inexpensive, easy to perform, tolerated well by patients
- Cells are destroyed by (cold) thermal damage
- 3 minute freeze/1 minute thaw/3 minute freeze well documented technique
- Does cause 2 -3 weeks of malodorous discharge
- Does hinder repeat colposcopy (SCJ often obscured)

LEEP

- Procedure of choice for most OB/GYN's
- Easy to perform, well tolerated and provides specimen for pathologic evaluation (Margins)
- Concern that multiple excisions or one large excision will increase rate of preterm labor/incompetent cervix

Preterm Delivery and LEEP

- Kyrgiou et al. Lancet 2006; 367: 489-98.
- Meta-analysis of 27 studies
- The studies chosen had to have a control group
- Evaluation of CKC, LEEP and laser for
  - Preterm delivery (<37 weeks gestation)
  - Low birth weight (<2500 g)
  - Cesarean delivery

- **CKC**
  - Preterm delivery- RR 2.59 (95% CI 1.80-3.72)
  - Low birth weight- RR 2.53 (95% CI 1.19-5.36)
  - Cesarean section- RR 3.17 (95% CI 1.07-9.40)
- **LEEP**
  - Preterm delivery- RR 1.70 (95% CI 1.24-2.35)
  - Low birth weight- RR 1.82 (95% CI 1.09-3.06)
  - Cesarean section- RR 2.69 (95% CI 1.62-4.46)
- **Laser**
  - NS for Preterm delivery- RR 1.71 (95% CI 0.93-3.14)

Preterm Delivery and LEEP

- **Summary**
- CKC patients are 2.5 times more likely to have a preterm delivery, low birth weight infant and/or cesarean section
- LEEP 1.5 times more likely
- Incidence of preterm delivery is 2-3%
  - CKC ~ 7.5% (1 in 15 women)
  - LEEP ~ 4.5% (1 in 20 women)

Preterm Delivery and LEEP

Margins and LEEP

- Margin status helpful in predicting recurrence of cervical dysplasia
- Negative margins ~15%
- Positive margins ~ 30-60%
- Re-excision not needed. Follow patient with serial Pap tests and treat accordingly if patient recurs

Dietrich, Obstet Gynecol 2002

Laser

- CO2 laser works by vaporizing cervical cells
- Very precise method; only need 5-7 mm of vaporization for treatment
- Heals great, spares cervical excisions
- COST major problem
- No pathology specimen

- Used to be the treatment of choice before LEEP
- Surgically excises dysplasia with scalpel/scissors
- Large cost to patient from physician, anesthesia and hospital charges
- Incompetent cervix an issue
- Indications to perform are few

Cold Knife Conization (CKC)

- The final treatment for cervical dysplasia
- Comes with significant morbidity/ mortality and lengthy recovery (6 weeks)
- Complications include: hemorrhage, infections, bowel & bladder injuries, MI, pulmonary embolus, stroke, death
- 10-20% of patients will continue to have abnormal pap tests: vaginal dysplasia

Hysterectomy

Efficacy of treatment

- Randomized controlled trial between cryosurgery, LEEP and laser showed no statistical difference in efficacy
- Recurrences were measure from 6-37 months
  - Cryosurgery 19%
  - LEEP 13%
  - Laser 13%

Mitchell, Obstet Gynecol 1998.

Which method to chose?

- Several factors to consider: age, desire for fertility, size of lesion, size of the cervix, severity of dysplasia and prior therapies
- Generalizations
  - Cryosurgery- best for young women with few finances and CIN 1 or 2
  - LEEP- the majority of women with CIN 2 or 3. Women with endocervical lesions also suited for LEEP

- Laser - women who have had multiple recurrences of CIN 2 or 3 and who want to retain fertility. Example: a 19 year old G_0 who has CIN 3, prior LEEP and a small cervix.
- CKC - glandular abnormalities (AIS) or early invasive cancer
- Hysterectomy - women finished with childbearing and who have persistent CIN. Often best utilized with other gynecologic problems like pelvic pain or abnormal uterine bleeding

Which method to chose?

- Repeat Pap testing at 6 and 12 months
  - ASC-US or greater = colposcopy (referral 63%)
  - 2 normal Pap tests = annual cytology screening
- High risk HPV testing at 12 months
  - Positive test = colposcopy
  - HPV 92% sensitive for detecting CIN 2-3 (referral 55%)
- Bottom line - more cost effective/less colposcopy with HPV testing

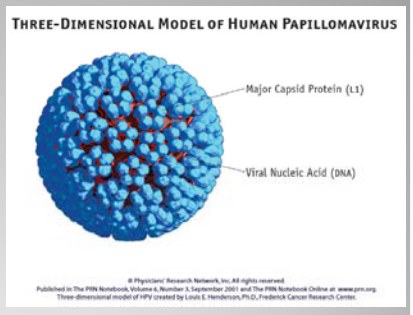
Post Procedure Surveillance

Guido et al. Am J Obstet Gynecol, 2003.

- HPV testing for post procedure surveillance is superior to cytology
  - Paraskevaidis et al. Cancer Treat Rev. 2004
  - Zielinski et al. Obstet Gynecol Surv. 2004
  - Cytology pooled sensitivity 70%
  - HPV pooled sensitivity 90%

Post Procedure Surveillance

- Quadrivalent HPV 6/11/16/18 L1 virus-like particle (VLP) vaccine.
- VLPs are produced in *Saccharomyces cerevisiae.*
  - The L1 proteins self-assemble into VLPs
  - Purified VLPs are adsorbed on aluminum-containing adjuvant
  - The adjuvant is amorphous aluminum hydroxyphosphate sulfate (225 µg per dose)
- Each 0.5-mL dose contains HPV Types 6/11/16/18 (20/40/40/20 µg L1 protein, respectively)



GARDASIL®: A Quadrivalent HPV Vaccine

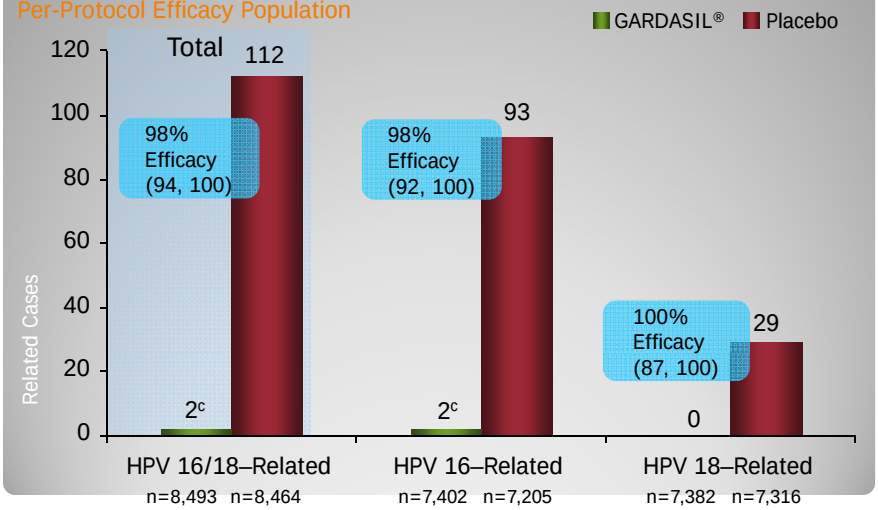
- Based on prespecified combined efficacy analysis of 4 phase 2/3 clinical trials[1–4]
  - More than 20,000 women (15–26 years) from the Americas, Europe and Asia were enrolled[1–4]
  - In one trial, subjects were randomized to either a monovalent HPV 16 L1 VLP vaccine or placebo[1]
  - In three trials, subjects were randomized to either GARDASIL® or placebo[2–4]
  - Vaccine or placebo was administered at day 1, month 2 and month 6[1–4]
  - Central pathology review[1–4]

End-of-Study Analysis for GARDASIL®

1. Mao C et al. *Obstet Gynecol.* 2006;107(1):18–27. 2. Villa LL et al. *Lancet Oncol.* 2005;6:271–278. 3. Garland SM et al. *N Engl J Med.* 2007;356(19):1928–1943; including supplementary material. 4. The FUTURE II Study Group. *N Engl J Med.* 2007;356(19):1915–1927.

GARDASIL®: Efficacy Against HPV 16– or 18–Related CIN[a] 2/3 or AIS[b]

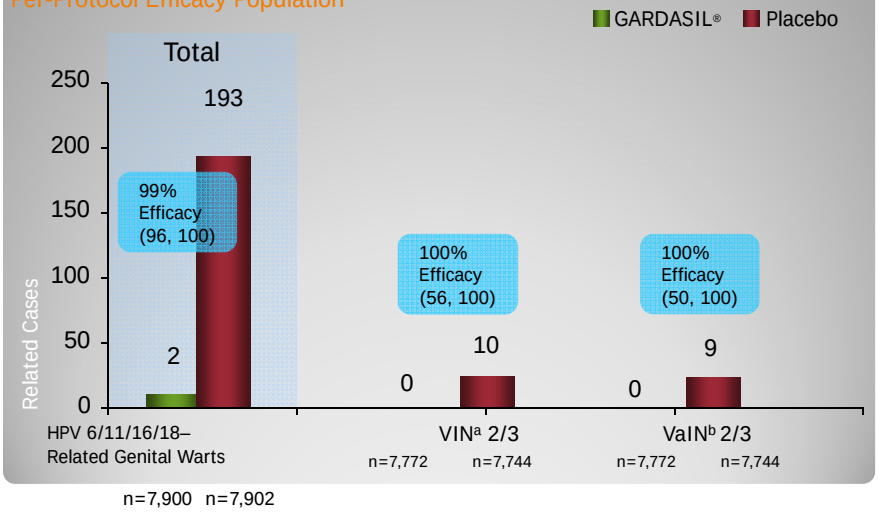
Per-Protocol Efficacy Population



[a]CIN = cervical intraepithelial neoplasia. [b]AIS = adenocarcinoma in situ.
[c]One case was a coinfection with HPV 52, the other was a coinfection with HPV 51 and 56.

GARDASIL®: Efficacy Against HPV 6/11/16/18 Related External Genital Lesions

Per-Protocol Efficacy Population

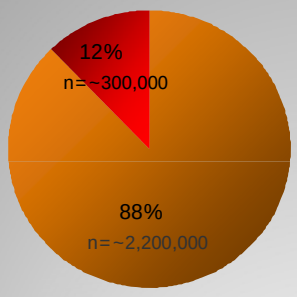


[a]VIN = vulvar intraepithelial neoplasia. [b]VaIN = vaginal intraepithelial neoplasia.

- Study of 3,276 sexually active women evaluated the use of risk factors to determine a young adult patient's appropriateness for HPV vaccination
- Identified risk factors that (1) could be assessed during an outpatient clinical encounter, and (2) were previously associated with either HPV-related cervical disease or HPV infection
  - Sex partner >2 years older
  - >3 lifetime sex partners
  - New sex partner in last 12 months
  - Illegal drug use in last 12 months
  - Sex while impaired by drinking
  - Never married

Risk-Based Vaccination Strategies

Dempsey AF et al. *Vaccine.* 2008;26(8):1111–1117.



% *without* current infection HPV 6, 11, 16, and/or 18

% *with* current infection HPV 6, 11, 16, and/or 18

- Of the estimated 2.5 million women with >3 sex partners
- 12% would already be currently infected with one or more HPV vaccine types.
  - 88% would not be currently infected with 6, 11, 16, and/or 18.
- The population-level impact of not vaccinating women with >3 lifetime sex partners means an estimated 2.2 million women who could potentially benefit would not be vaccinated.

Estimated Population-Level Impact of Not Vaccinating Women With >3 Lifetime Sex Partners

Dempsey AF et al. *Vaccine.* 2008;26(8):1111–1117.

- Risk-factor–based vaccination would cause HPV vaccines to be withheld from a large number of women without evidence of current infection
- Identification of individuals based on either the presence or absence of risk factors does not appear to be a viable strategy for HPV catch-up vaccination of young adults
- The ACIP does not recommend a risk-based immunization strategy for HPV vaccination

Risk-Based Vaccination Strategies: Study Conclusion

Dempsey AF et al. *Vaccine.* 2008;26(8):1111–1117.

Injection Site (1 to 5 Days Postvaccination)			
	GARDASIL® (N=5,088)	Placebo (Aluminum) (N=3,470)	Placebo (Saline) (N=320)
Pain	83.9%	75.4%	48.6%
Swelling	25.4%	15.8%	7.3%
Erythema	24.6%	18.4%	12.1%
Pruritus	3.1%	2.8%	0.6%
Systemic (1 to 15 Days Postvaccination)			
		GARDASIL® (N=5,088)	Placebo (N=3,790)
Fever		10.3%	8.6%
Nausea		4.2%	4.1%
Dizziness		2.8%	2.6%

- Few subjects (0.1%) discontinued due to adverse experiences.

The table shows the vaccine-related adverse experiences that were observed among recipients of GARDASIL® at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.

Vaccine-Related Adverse Experiences

- Females age 11-12
- Females as young as 9 may receive HPV vaccination
- Vaccination is also recommended to females age 13-18 to catch up missed vaccine or to complete the series
- Vaccination is not currently recommended for women over the age of 26 or for males
- Screening for cervical cancer should continue in both vaccinated and unvaccinated women

American Cancer Society recommendations for HPV vaccination

Saslow et al. Cancer J Clin. 2007.

Summary of US Vaccine Recommendations

Recommendations	ACIP[1,a]	ACOG[2,b]	AAFP[3,c]	AAP[4,d]
Routine vaccination in females 11–12 years old and catch-up vaccination in 13- to 26-year-olds	✓	✓	✓	✓
Females 9–10 years old can be vaccinated	✓	✓	✓	✓
Vaccinate regardless of previous HPV infection or abnormal Pap test results	✓	✓	✓	✓
Continue Pap testing after vaccination	✓	✓	✓	✓

[a]ACIP = Advisory Committee on Immunization Practices.
[b]ACOG = American College of Obstetricians and Gynecologists.
[c]AAFP = American Academy of Family Physicians.
[d]AAP = American Academy of Pediatrics.

1. Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep.* 2007;56(RR-2):1–24. 2. American College of Obstetricians and Gynecologists (ACOG). *Obstet Gynecol.* 2006;108(3):699–705. 3. Department of Health and Human Services, Centers for Disease Control and Prevention. Recommended immunization schedule for persons aged 7–18 years, United States, 2008. http://www.cispimmunize.org/IZSchedule_ Adolescent.pdf. Accessed July 14, 2008. 4. Committee on Infectious Diseases. *Pediatrics.* 2007;120(3);666–668.

- If it is best to administer HPV vaccination prior to coitarche, when are adolescents engaging in sexual activity?
  - Abma et al. Vital Health Stat. 2004
  - 24% of females are sexually active by 15
  - 40% by age 16
  - 70% by age 18
  - Grunbaum et al. Surveill Summ. 2004
  - 7% of high school students (males and females) reported coitarche before 13
  - 10% of 9th graders (14-15) reported having more than 4 partners

Age to Vaccinate

Duration of Protection

- Harper et al. Lancet. 2006
  - Bivalent vaccine HPV 16/18
  - 98% seropositivity for 4.5 years
  - 96.9% reduction in HPV 16/18
- Villa et al. Br J Cancer. 2006
  - Quadrivalent HPV 6/11/16/18
  - 100% seropositivity for 5 years
  - 96% reduction in HPV 6/11/16/18
    - (2 vaccine/ 46 placebo)

HPV Vaccination of Males

- Efficacy trials are ongoing with males 9-15 (Gardasil®)
- If efficacious the vaccine would prevent
  - Anogenital warts in males and indirect transmission to women
  - Penile, anal, oral and head and neck cancers
  - Juvenile respiratory papillomatosis
- Data should be released next month

Summary

- HPV is ***THE*** cause of cervical cancer and dysplasia
- Majority of men and women will have been exposed to HPV before the age of 50
- Smoking is an important co-factor in oncogenesis
- Vaccinations are effective in preventing HPV infections and histologic abnormalities

Summary of Abnormal Squamous Pap Tests

- ASC-US
  - Repeat cytology in 6 months
  - HPV testing
  - Colposcopy
- LSIL/ASC-H
  - Colposcopy
- HSIL
  - Colposcopy
  - LEEP

Summary of Abnormal Glandular Pap Tests

- AGC Pap tests
  - Colposcopy
  - ECC
  - Endometrial biopsy (women >35 or with menorrhagia)
- AIS
  - Referral to a gynecologist or a gynecologic oncologist

Summary of CIN

- CIN 1
  - Serial cytology at 6 and 12 months
  - HPV testing in 12 months
- CIN 2-3
  - LEEP